RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) FACTORS FOR USE IN CALCULATING PROBABILITY OF CAUSATION OF RADIOGENIC CANCERS

David C. Kocher, A. Iulian Apostoaei, and F. Owen Hoffman
SENES Oak Ridge, Center for Risk Analysis[1]

INTRODUCTION

This report presents relative biological effectiveness (RBE) factors for different types of ionizing radiations for use in calculating the probability of causation of specific cancers in humans. The RBE factors developed in this report are expressed as probability distributions which are intended to represent uncertainties in relevant radiobiological data and other judgments involved in evaluating available information. The ionizing radiations of concern include photons (gamma rays and *X* rays),[2] electrons, alpha particles, and neutrons. Except in cases of exposure of the lung to alpha particles emitted by the short-lived decay products of radon in air, the probability distributions of RBE factors are intended to be applied in calculating the probability of causation of radiogenic cancers in any organ or tissue and for any exposure situation.[3]

The probability distributions of RBE factors developed in this report are intended to represent differences in the biological effectiveness of different radiation types in causing stochastic effects in humans, primarily cancers. RBE factors take into account that, for a given absorbed dose in tissue, the probability of a stochastic response depends on the radiation type, and sometimes its energy, as well as the absorbed dose. For a particular radiation of concern, the probability distribution of the RBE factor represents data on RBE obtained from relevant radiobiological studies. The RBE of radiation i compared with a reference radiation, r, is defined as the absorbed dose of the reference radiation (D_r) required to produce a specific level of response relative to the absorbed dose of the radiation of concern (D_i) required to produce an equal response:

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[1]*SENES* Oak Ridge, Inc., Center for Risk Analysis, 102 Donner Drive, Oak Ridge, TN 37830. Phone, (865)483-6111; fax, (865)481-0060; email, senesor@senes.com. Research sponsored by National Institute of Occupational Safety and Health (NIOSH) under contract with *SENES* Oak Ridge, Inc.

[2]Gamma rays are electromagnetic radiations emitted in de-excitation of atomic nuclei, whereas *X* rays are electromagnetic radiations emitted in de-excitation of atomic electrons, referred to as characteristic *X* rays, or electromagnetic radiations produced in deceleration of charged particles (e.g., electrons) in passing through matter, referred to as continuous *X* rays or bremsstrahlung.

[3]The probability of causation of lung cancer due to inhalation of radon and its short-lived decay products is calculated based on an estimate of the risk per unit exposure to the short-lived alpha-emitting decay products in Working Level Months (WLM), and an RBE factor for alpha particles that would be applied to estimates of absorbed dose in the lung is not used.

$$\mathrm{RBE}_i = \frac{D_r}{D_i}, \quad (1)$$

with all physical and biological variables, except differences in radiation type, being held as constant as possible. Values of RBE are specific to each study, and they generally depend on the biological system and specific response under study, the magnitude of the absorbed doses, the dose rate, and the dose per fraction if the dose is fractionated.[4]

In most radiobiological studies in which RBEs were estimated, the reference radiation was either orthovoltage *X* rays (usually 180-250 kVp)[5] or higher-energy gamma rays produced in the decay of ^{60}Co (photon energies of 1.2 and 1.3 MeV) or, less frequently, ^{137}Cs (0.66 MeV). Knowledge of the reference radiation in any study is important because, as discussed in this report, the biological effectiveness of *X* rays apparently is greater than that of higher-energy gamma rays. In this report, the reference radiation is taken to be high-energy gamma rays, specifically the gamma rays emitted in ^{60}Co decay. This choice is appropriate for the purpose of developing RBE factors for use in calculating the probability of causation of cancers because estimates of cancer risks in humans are based primarily on data obtained from studies of the Japanese atomic-bomb survivors who were exposed mainly to high-energy gamma rays.[6]

The probability distributions of RBE factors in humans presented in this report are based primarily on published reviews and evaluations of radiobiological studies. For the most part, we relied on reviews by such expert groups as the International Commission on Radiological Protection (ICRP), the International Commission on Radiation Units and Measurements (ICRU), the National Council on Radiation Protection and Measurements (NCRP), the U.K.'s National Radiological Protection Board (NRPB), and the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC), as well as reviews by individuals who are recognized experts. We used other information from the primary literature only to a limited extent.

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[4]Although the term "RBE factor" is used in this report to describe the biological effectiveness of different radiations in inducing cancers in humans, we recognize that these factors are not true RBEs. In accordance with the definition given above, the term "RBE" strictly applies only to the results of specific radiobiological studies, but RBE factors in humans generally are assumed values that are based on evaluations of studies in other biological systems.

[5]The term "kVp" denotes the maximum potential difference in kilovolts (kV) across an *X*-ray tube during an exposure; this potential difference determines the maximum electron energy in keV. The average energy of the continuous spectrum of bremsstrahlung produced when the electrons are stopped in a target is a small fraction of the peak tube potential in kVp.

[6]At the present time, the only cancer risks that are not estimated based on data in the Japanese atomic-bomb survivors, in addition to the risks of lung cancer from inhalation of radon and its short-lived decay products, are the risks of thyroid cancer resulting from exposure in childhood (Land et al., 2002). These risks are estimated based primarily on studies of children who were exposed to *X* rays.

The probability distributions of RBE factors developed in this report are intended to represent uncertainties in values that should be used to calculate the probability of causation of radiogenic cancers. It cannot be overemphasized that the development of these probability distributions relies to a significant extent on subjective scientific judgment. The most important judgment is an assumption that RBEs obtained from studies of a number of stochastic responses in a variety of biological systems are applicable to induction of cancers in humans. This assumption is necessitated by the lack of data on RBEs for cancer induction in humans. Scientific judgment also is applied by experts and expert groups in their reviews and evaluations of published studies, and in the conclusions they draw from these reviews. Finally, we have applied our own scientific judgments in developing probability distributions of RBE factors, and we recognize that knowledgeable individuals could reach somewhat different conclusions based on the same body of information.

In this report, we have assumed that the probability distributions of RBE factors apply to all cancers. We have not explicitly taken into account the possibility that the biological effectiveness of some radiations may depend on the particular cancer of concern. For example, in some studies of neutrons and alpha particles, RBEs for leukemias and lymphomas appear to be less than RBEs for solid tumors (NCRP, 1990; Muirhead et al., 1993; EPA, 1994; Edwards, 1997; Edwards, 1999). We have accounted for such differences only in a general way by developing probability distributions of RBE factors that are sufficiently broad to encompass available data for all stochastic responses studied.

In developing probability distributions of RBE factors for use in calculating the probability of causation of radiogenic cancers, an important consideration is the extent to which these distributions should be consistent with recommendations developed by national and international advisory groups for purposes of radiation protection. In radiation protection, the quantities that are analogous to an RBE factor are the effective quality factor, $\overline{Q}$ (ICRU, 1986), and the radiation weighting factor, w_R (ICRP, 1991; NCRP, 1993).[7]

Effective quality factors and radiation weighting factors used in radiation protection are prescribed point values that are intended to represent relevant data on RBE. For the radiation types considered in this report, the values of $\overline{Q}$ recommended by the ICRU (1986), which were developed by a Joint Task Group of the ICRP and the ICRU, and the values of w_R currently recommended by the ICRP (1991) and the NCRP (1993) are given in Table 1. Although there is general agreement between the two sets of recommendations, there are some differences, especially in the recommendations for photons of energy less than 30 keV and low-energy beta particles emitted in the decay of tritium (^{3}H). There also are smaller differences in the recommendations for alpha particles and neutrons.

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[7]The effective quality factor is intended to be applied to the radiations at the locations in tissue where an absorbed dose is delivered, whereas the radiation weighting factor is intended to be applied to the radiations incident on the body or the radiations emitted by internally deposited radionuclides.

Although consistency between the RBE factors developed in this report and the effective quality factors and radiation weighting factors recommended by national and international authorities may be desirable, there are two important factors to be considered. First, point estimates of radiation protection quantities do not reveal the state of knowledge (uncertainty) in these values, including uncertainties in the RBEs obtained from relevant radiobiological studies and uncertainties in other judgments used to develop the point estimates. A full accounting of uncertainties in all parameters is essential when estimating probability of causation for the purpose of evaluating claims by individuals that their cancer was caused by radiation exposure.

Second, for some radiations, it is evident that the recommended point values of radiation protection quantities given in Table 1 are not consistent with the preponderance of relevant radiobiological information. For example, the ICRU (1986) concluded that there is clear evidence that the biological effectiveness of orthovoltage *X* rays and other photons of energy less than about 0.2 MeV is about twice that of high-energy ^{60}Co gamma rays. This conclusion was based on a review of data on RBEs for orthovoltage *X* rays and a calculation of the energy dependence of the effective quality factor for photons shown in Fig. 1. Nonetheless, neither the ICRU nor the ICRP and the NCRP have incorporated this difference in their recommendations on radiation protection. Similarly, the ICRP and the NCRP have not taken into account the clear evidence from available data and a calculation by the ICRU (1986) that beta particles emitted in decay of ^{3}H are biologically more effective than higher-energy electrons and photons.

It is important to recognize that the needs of radiation risk assessment and calculations of probability of causation in cases where actual exposures of specific individuals are of concern differ significantly from the needs of radiation protection. The primary concern in radiation protection is control of exposures based on evaluations of compliance with applicable limits on radiation dose and other radiation protection requirements, but without undue concern for actual doses and risks to exposed individuals and their uncertainties. The use of standard and simplified assumptions for this purpose is appropriate. However, as noted above, estimates of probability of causation must be based on the state of knowledge of actual doses and risks to exposed individuals. Thus, although we have relied on reviews and evaluations of available radiobiological data by such groups as the ICRU, the ICRP, and the NCRP, we have not assumed *a priori* that the effective quality factors or radiation weighting factors given in Table 1 provide "best" estimates of RBE factors for use in calculating probability of causation. As discussed in the following sections, the probability distributions of RBE factors for neutrons and alpha particles developed in this report encompass the recommended values of radiation protection quantities in Table 1, but the probability distributions of RBE factors for lower-energy photons and electrons depart substantially from the recommendations of the ICRP and the NCRP.

The following sections present the probability distributions of RBE factors for neutrons, alpha particles, photons, and electrons. Neutrons are discussed first because they have been the most studied and alternative approaches to estimating RBEs have been developed. An understanding of these approaches is useful in developing RBE factors for the other radiations.

RBE FACTORS FOR NEUTRONS

Approaches to Estimating RBEs

RBEs for neutrons have been estimated in many studies involving different organisms, stochastic endpoints (responses), and doses and dose rates. Most studies used fission neutrons or other neutrons of comparable energies; relatively few studies used neutrons of lower or higher energies. Extensive reviews and evaluations of these data have been presented by the ICRU (1986), the NCRP (1990), and the NRPB (Edwards, 1997).

In most studies, the doses and dose rates of neutrons and the reference radiations were substantially above levels that are encountered in routine exposures of workers and the public. Furthermore, as illustrated in Fig. 3, RBEs for neutrons generally increase with decreasing dose. Therefore, an important focus of radiobiological studies and reviews by expert groups has been to develop estimates of RBE that are appropriate at low doses and dose rates. These RBEs are obtained by extrapolation of data on dose-response for neutrons and the reference radiation at higher doses and dose rates. An RBE at low doses and dose rates obtained by this extrapolation usually is denoted by RBE_M. Summaries of estimated values of RBE_M for fission neutrons developed by the ICRU (1986) and the NCRP (1990) are given in Table 2.[8]

From an evaluation of values of RBE_M obtained from different studies that are deemed relevant to estimating cancer risks in humans, a representative RBE factor at low doses and low dose rates, denoted by $\overline{RBE}_M$ in this report, is chosen.[9] This estimate is a point value for purposes of radiation protection (e.g., a radiation weighting factor, w_R), but is expressed as a probability (uncertainty) distribution for purposes of estimating cancer risks and probability of causation in cases of exposure of specific individuals. Using the RBE at low doses and low dose rates, the cancer risk per unit absorbed dose, R, at low doses and dose rates can be estimated as

$$R = \overline{RBE}_M \times \frac{R_{\gamma,H}}{DDREF_\gamma} , \qquad (2)$$

where $R_{\gamma,H}$ is the cancer risk per unit absorbed dose at high doses and high dose rates of gamma rays (e.g., the excess relative risk, ERR, per Gy, as estimated mainly from studies of the Japanese

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[8]In some cases including, for example, the evaluation of data on tumor induction by the NCRP (1990), values of RBE_M obtained in some studies lie outside the range given in Table 2. Furthermore, the ranges in Table 2 generally are based on central estimates of RBE_M, and values outside these ranges cannot be ruled out when uncertainties in the estimates are taken into account.

[9]We denote an assumed RBE factor for induction of cancers in humans by $\overline{RBE}$ to distinguish this quantity from an RBE obtained from a specific study in a particular biological system and to indicate that an RBE factor is intended to represent a variety of RBEs obtained from different studies.

atomic-bomb survivors) and $DDREF_\gamma$ is the dose and dose-rate effectiveness factor, which takes into account that cancer risks per unit dose at low doses and low dose rates of gamma rays (and other low-LET radiations) may be less than risks per unit dose at high doses and high dose rates in study populations. For example, for purposes of radiation protection, the ICRP (1991) and the NCRP (1993) currently recommend a $DDREF_\gamma$ of 2; i.e., estimated cancer risks per unit dose in the atomic-bomb survivors are reduced by a factor of 2 in estimating risks from exposure to gamma rays and other low-LET radiations at lower doses and dose rates. As indicated by the summary in Table 2, the values of RBE_M for fission neutrons obtained from different studies vary widely. Thus, a probability distribution of $\overline{RBE}_M$ that would represent these data for purposes of calculating probability of causation would span a wide range of values.

In most studies, the dose-response relationship for neutrons is linear at absorbed doses of a few Gy or less, whereas the dose-response relationship for the low-LET reference radiation is linear-quadratic in form (ICRU, 1986; NCRP, 1990); see Fig. 4. Thus, the variability in values of RBE_M for neutrons obtained from different studies is due in part to pronounced differences in the linear-quadratic dose-response relationships for the reference radiations, which result in a wide range of DDREFs for these radiations when calculated as shown in Fig. 5 (CIRRPC, 1995; Edwards, 1997; Edwards, 1999). That is, RBE_M is sensitive to variations in the biological effectiveness at low doses of the reference radiations, with higher values of RBE_M associated with high DDREFs and lower values with low DDREFs. Since the DDREFs for the reference radiations embodied in the values of RBE_M for neutrons generally are not the same as the value of $DDREF_\gamma$ that might be used to adjust observed cancer risks in humans at high doses and high dose rates of gamma rays to obtain estimates of risk at low doses and low dose rates, a probability distribution of $\overline{RBE}_M$ that is based on the variability in estimates of RBE_M may not provide the best representation of the biological effectiveness of low doses of neutrons in humans relative to low doses and dose rates of gamma rays.

For the purpose of estimating probability of causation of cancers at low doses and dose rates of neutrons, difficulties with developing a representative probability distribution of $\overline{RBE}_M$ based on estimates of RBE_M obtained from different studies can be addressed by using an alternative approach recommended by CIRRPC (1995) and discussed by Edwards (1997; 1999). This approach is based on an assumption that RBE factors for neutrons in humans should be consistent with the data used to estimate cancer risks from exposure to photons. That is, the appropriate RBE factors are values obtained from studies in which the reference radiations were gamma rays at high doses and high dose rates, because this was the condition of exposure of the Japanese atomic-bomb survivors from which most estimates of cancer risks in humans have been derived. Thus, if the DDREF for neutrons is assumed to be unity, based on the observation that the dose-response relationship usually is linear at absorbed doses of a few Gy or less and the usual presumption of linearity at low doses for all high-LET radiations, the risk per unit absorbed dose from exposure to neutrons at low doses and low dose rates can be estimated as

$$R = \overline{RBE}_H \times R_{\gamma,H} , \qquad (3)$$

where $\overline{RBE}_H$ is the probability distribution of the RBE factor that represents data on RBE for neutrons at high acute doses of the reference radiation and $R_{\gamma,H}$ again is the risk per unit absorbed dose at high doses and high dose rates of gamma rays. In this approach, the cancer risk does not depend on the value of $DDREF_\gamma$ in humans. Since the DDREF for neutrons is assumed to be unity, eq. (3) also applies at high doses and high dose rates of neutrons.

When the approach in eq. (3) is used to estimate risk, there still is considerable variability in estimates of RBE for neutrons at high acute doses of the reference radiations, RBE_H. This variability is due to several factors including the variety of biological systems and stochastic endpoints studied, as well as the dependence of RBE on dose (see Figs. 3 and 4). However, the variability in RBE_H is considerably less than the variability in RBE_M, due mainly to the reduced influence at high doses of differences in the DDREFs for the reference radiations. Therefore, the uncertainty in a representative value of $\overline{RBE}_H$ should be less than the uncertainty in $\overline{RBE}_M$.

It is important to emphasize that estimates of cancer risks at low doses and dose rates of neutrons obtained using eq. (3) would be the same as risks estimated using eq. (2) if the values of DDREF for the reference radiations embodied in the values of RBE_M were the same as the value of $DDREF_\gamma$ that is used to adjust observed risks at high doses and high dose rates of gamma rays in humans to obtain estimates of risk at low doses and low dose rates. The advantage of using the approach in eq. (3) is that it is directly compatible with the data in the Japanese atomic-bomb survivors who were exposed at high doses and high dose rates. Again, these are the data from which most estimates of cancer risks in humans are obtained.

RBE Factor for Fission Neutrons

Based on the discussion of alternative approaches to estimating RBEs for neutrons, we develop a probability distribution of $\overline{RBE}_H$ for fission neutrons to be used in estimating cancer risks at any dose and dose rate in accordance with eq. (3). This probability distribution is developed based on the results of an analysis of RBEs at high acute doses of the reference radiations by Edwards (1999); see also a report of the NRPB (Edwards, 1997). Values of RBE_H derived by Edwards (1999) from an analysis of data obtained in several studies of life-shortening and induction of specific cancers in mice are summarized in Tables 3-5.[10] Since life-shortening in mice was due mainly to induction of cancers, the different endpoints are closely related. Values of RBE_M derived by Edwards also are given in the tables. In all studies summarized in these tables, the reference radiation was high-energy gamma rays.

The data in Tables 3-5 illustrate two points discussed previously. First, RBEs at high doses and dose rates generally are less than the corresponding extrapolated values at low doses and dose rates, due primarily to the influence of the DDREF for the reference radiation on the

[10]Values of RBE_H given by the NRPB (Edwards, 1997) incorporate an assumed DDREF of 2 for the reference radiations and, thus, are a factor of 2 higher than the values given in the later paper by Edwards (1999). The values in Edwards (1999) are the appropriate ones for use in eq. (3).

extrapolated values. Second, the variability in RBE_H is less than the variability in RBE_M, due primarily to the reduced influence of differences in the DDREFs for the reference radiations in the various studies. For example, in the studies summarized in Tables 3 and 4, the DDREF for the reference radiation, as estimated by the ratio of the mean value of RBE_M to the mean value of RBE_H, varies from 1 to nearly 20.

Life-shortening and induction of specific cancers in mice should be especially relevant to estimating RBE factors for cancers in humans. Therefore, based on the estimates of RBE_H and their standard errors summarized in Tables 3-5, we describe the RBE factor, $\overline{RBE}_H$, for fission neutrons to be used in eq. (3) by a lognormal probability distribution having a 95% confidence interval between 1.5 and 30. This distribution has a geometric mean and geometric standard deviation of 6.7 and 2.2, respectively, and an arithmetic mean of 9.0. A lognormal probability distribution was selected based mainly on the variability in the estimates of RBE_H and the difficulty in judging a credible upper bound of possible values. Truncation of the lower tail of the distribution at 1.0, based on an assumption that the biological effectiveness of neutrons should not be less than that of high-energy gamma rays, is discussed later in this section. The assumed probability distribution of $\overline{RBE}_H$ for fission neutrons applies to a spectrum of energies that ranges from 0.1-15 MeV; this spectrum has a most probable energy of 0.8 MeV and an average energy of 2.0 MeV (Shleien et al., 1998).

Data obtained from studies of tumor induction in other animals are consistent with the probability distribution of $\overline{RBE}_H$ for fission neutrons described above. For example, Wolf et al. (2000) deduced an RBE of about 20-25 for induction of lethal tumors in Sprague-Dawley rats at an acute dose of fission neutrons of 0.1 Gy. In a study in which monkeys were given average doses of 6.7 Gy of *X* rays and 3.4 Gy of fission neutrons, Broerse et al. (1991) derived an RBE for tumor induction of about 4-5. When this value is adjusted to account for the difference of about a factor of 2 in the biological effectiveness of *X* rays and gamma rays, as discussed in a later section, an RBE relative to gamma rays of about 8-10 is obtained. Other studies of tumor induction in animals are discussed by the NCRP (1990).

The probability distribution of $\overline{RBE}_H$ for fission neutrons can be compared with the effective quality factor, $\overline{Q}$, for neutrons of unknown energy recommended by the ICRU (1986) and the radiation weighting factor, w_R, for neutrons of energy 0.1-2 MeV recommended by the ICRP (1991) and the NCRP (1993); see Table 1. The point values of $\overline{Q}$ and w_R are based on estimates of RBE_M and, thus, would be used to estimate cancer risks in accordance with eq. (2). If we assume a $DDREF_\gamma$ of 2 as normally used in radiation protection (ICRP, 1991; NCRP, 1993), the probability distribution of $\overline{RBE}_H$ would correspond to a distribution of $\overline{RBE}_M$ having a 95% confidence interval between 3 and 60.[11] Therefore, the probability distribution of $\overline{RBE}_H$

[11]This confidence interval does not represent the range of values of RBE_M for fission neutrons obtained from analyses of different radiobiological studies, because DDREF for the reference radiation often differed greatly from the value of 2 assumed here. As illustrated in Tables 3-5, upper confidence limits of RBE_M considerably greater than 60 are obtained in some studies (see also Table 2).

for fission neutrons, when multiplied by a $DDREF_\gamma$ of 2, encompasses the point values of quantities that have been recommended for use in radiation protection.[12]

Consideration of Cancer-Specific RBEs

The probability distribution of $\overline{RBE}_H$ for fission neutrons described above is intended to be applied to all cancers in humans. However, some studies in animals suggest that RBEs for leukemias and lymphomas are less than RBEs for solid tumors (NCRP, 1990; Edwards, 1997; Edwards, 1999). Such a difference is indicated, for example, by estimates of RBE_H and RBE_M for specific cancers in RF/Un and RFM mice given in Table 4.

In this report, we have not developed separate probability distributions of RBE factors for leukemias or lymphomas and solid tumors, mainly because a significant difference in RBEs is not shown in all studies. For example, RBEs for myeloid leukemia in CBA/H mice given in Table 4 are about the same as RBEs for solid tumors in BALB/c and SAS/4 mice. Furthermore, the central estimates of RBE_H from all studies given in Table 4 suggest that the difference in RBEs for leukemias and solid tumors is no more than about a factor of 2. Similarly, the results of a study using B6CF1 mice given in Table 5 do not show a significant difference in RBEs for lymphocytic tumors and other tumors. We have accounted for possible cancer-specific differences in RBEs for fission neutrons only in a general way by defining the probability distribution of $\overline{RBE}_H$ so that the 95% confidence interval encompasses the full range of estimates of RBE_H and their uncertainties given in Tables 3-5.

RBE Factors at Other Energies

Estimation of cancer risks in humans from exposure to neutrons is complicated by the apparent dependence of RBEs on neutron energy. This energy dependence is represented by the radiation weighting factors currently recommended by the ICRP (1991) and the NCRP (1993) for use in radiation protection (see Table 1 and Fig. 6). In comparison, the quality factors at different neutron energies currently used by the U.S. Nuclear Regulatory Commission (NRC, 1991) and the U.S. Department of Energy (DOE, 1993) are given in Table 6. These quality factors were developed by the NCRP (1971) based on calculated depth-dose distributions in a cylindrical phantom or tissue slab at incident neutron energies of 0.025 eV to 400 MeV. The recommended radiation weighting factors and the quality factors used by regulatory authorities indicate that the probability distribution of $\overline{RBE}_H$ for fission neutrons described above applies at energies that have the highest biological effectiveness.

The reductions in the radiation weighting factor at neutron energies outside the range of 0.1-2 MeV recommended by the ICRP (1991) and the NCRP (1993) are based mainly on limited

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[12]The point values of $w_R = 20$ and $\overline{Q} = 25$ in Table 1 are at about the 70th and 80th percentiles, respectively, of this probability distribution.

data obtained from studies in animals and cell cultures, which are reviewed by the NCRP (1990) and the NRPB (Edwards, 1997), and calculations of the quality factor vs. neutron energy, such as those given in Fig. 2 (ICRU, 1986) and Table 6 (NCRP, 1971). Other studies of the energy dependence of the biological effectiveness of neutrons are discussed by the NCRP (1990) and Edwards (1997). The ICRP (1991) also suggested that its recommended step function for the radiation weighting factor given in Table 1 can be represented by a smooth function of the form

$$w_R = 5 + 17\exp[-(\ln(2E))^2/6] \ , \qquad (4)$$

where E is the neutron energy in MeV. This relationship is not intended to imply any biological significance, but it does provide a convenient calculational tool when incident neutron energies are well known. The smooth function in eq. (4) is compared with the recommended step function for the radiation weighting factor in Fig. 6.

We define the energy dependence of the RBE factor for neutrons, $\overline{\mathrm{RBE}}_H$, to be used in eq. (3) in the following way. In the ICRP's step-function representation of w_R given in Table 1 and Fig. 6, the values at energies other than 0.1-2 MeV are a factor of 2 or 4 less than the value that applies to fission neutrons. Thus, as a first approximation, when neutron energies are outside the range of 0.1-2 MeV, the probability distribution of $\overline{\mathrm{RBE}}_H$ for fission neutrons could be reduced by a factor of 2 or 4, depending on the energy. For example, a reduction by a factor of 2 would apply to 14-MeV neutrons produced by the ^{3}H(d,n)^{4}He reaction at low projectile energies, and a reduction by a factor of 4 would apply to thermal neutrons.

However, uncertainties in the energy-dependent reduction factors also should be taken into account. Based on data shown in Figs. 7 and 8 and other data reviewed by the NRPB (Edwards, 1997) and the NCRP (1990), we represent the reduction factor at neutron energies of 10-100 keV or 2-20 MeV by a lognormal probability distribution having a 95% confidence interval between 1.0 and 4.0. This distribution has a geometric mean and geometric standard deviation of 2.0 and 1.4, respectively, and an arithmetic mean of 2.1. Based on calculations by the NCRP (1971) which indicate that the biological effectiveness should decrease as the neutron energy decreases below 10 keV or increases above 20 MeV, we then represent the reduction factor at these energies by a lognormal probability distribution having a 95% confidence interval between 2.0 and 8.0. The geometric and arithmetic means of this distribution are twice the values given above, and the geometric standard deviation is the same.

The probability distributions of the energy-dependent reduction factors described above represent assumptions that the values probably differ from the central estimates of 2 or 4 by no more than a factor of 2, and that values above and below the central estimates are equally likely. However, the assumed distributions also give a small weight to the possibility that the reduction factors differ from the central estimates by more than a factor of 2. For example, the probability distribution of the reduction factor at neutron energies of 10-100 keV gives a weight of 2.5% to an assumption that the RBE factor is somewhat higher than the value at energies of 0.1-2 MeV. This assumption is supported by the data summarized in Fig. 7 and by the results of a study by

Miller et al. (2000) which indicated that the biological effectiveness of 70-keV and 350-keV neutrons was not significantly different. Uncertainties in these reduction factors should be smaller than the uncertainty in $\overline{\text{RBE}}_{\text{H}}$ for fission neutrons.

Correction for Inverse Dose-Rate Effect

An additional consideration in estimating cancer risks from exposure to neutrons is the possibility that the biological effectiveness of neutrons, and other high-LET radiations, increases as the dose rate decreases. This phenomenon is referred to as the inverse dose-rate effect. Some studies of life-shortening and tumor induction in small mammals at relatively high doses of fission neutrons reviewed by the NCRP (1990), the ICRP (1991), and CIRRPC (1995) show an enhancement in biological effectiveness by as much as a factor of about 3 when the same dose is delivered at lower dose rates. However, this effect is not seen in all studies of these endpoints at high doses, and it usually is not seen at lower doses.

Although it is not clear whether the mechanisms responsible for the observed inverse dose-rate effect for fission neutrons in some studies would apply in estimating cancer risks in humans, especially at low doses (CIRRPC, 1995), we apply a small correction factor to account for this effect. This correction, which we refer to as an enhancement factor, is applied only in cases of chronic exposure to neutrons of any energy; it does not apply to acute exposures.

Based on discussions and summaries of data on life-shortening and tumor induction in small mammals given in Sections 6 and 8 and Tables 6.2 and 8.2 of NCRP (1990), we assume a probability distribution for the enhancement factor representing the inverse dose-rate effect under conditions of chronic exposure to neutrons that ranges from 1 to 3 and is weighted toward lower values. Specifically, we assume a discrete probability distribution with 50% of the values at 1.0, 30% at 1.5, 15% at 2.0, and 5% at 3.0. The arithmetic mean of this distribution is 1.4. This distribution takes into account that the effect is not seen in all studies at high doses and usually is not seen at low doses of greatest interest in routine exposures of workers and the public.

Summary

Cancer risks in humans at any dose and dose rate of neutrons are estimated using an approach represented by eq. (3). Specifically, the risk per unit absorbed dose from exposure to neutrons (n) is estimated as

$$R_n = \overline{\text{RBE}}_{n,\text{H}} \times \text{AF}_n \times \text{EF}_n \times R_{\gamma,\text{H}} , \qquad (5)$$

where $\overline{\text{RBE}}_{n,\text{H}}$ is the RBE factor for fission neutrons at high doses and high dose rates of gamma rays, AF_n is an energy-dependent adjustment factor that represents the reduction in biological effectiveness of neutrons when the energy is outside the range of 0.1-2 MeV, EF_n is an enhancement factor that represents the inverse dose-rate effect for chronic exposure to neutrons of any energy, and $R_{\gamma,\text{H}}$ is the risk per unit dose at high doses and high dose rates of gamma rays.

Thus, the biological effectiveness of neutrons relative to high doses and high dose rates of gamma rays is represented by a combination (aggregate) of up to three probability distributions that take into account the different factors of concern and their uncertainties.

Given the assumed probability distributions of each of the factors summarized above, the probability distribution of the RBE factor for neutrons in specific cases will include some values less than 1.0. In all cases, however, the lower tail of the aggregate probability distribution should be truncated at 1.0. This truncation is based on an assumption that, since some of the dose due to incident neutrons of any energy would be delivered by high-LET radiations (NCRP, 1971; ICRP, 1997), the biological effectiveness of neutrons should not be less than that of high-energy gamma rays. The lower tail should be truncated only after the aggregate probability distribution representing the combination of all relevant factors contributing to the RBE factor for a given exposure situation is obtained.

It is possible that the RBE factor for neutrons in humans could be less than 1.0 when most of the dose is delivered by the 2.2-MeV gamma rays emitted following capture of thermalized neutrons by ^{1}H nuclei. This situation could occur when the incident neutron energy is less than about 10 keV (NCRP, 1971). The possibility of an RBE factor less than 1.0 at low energies is based on the consideration that the biological effectiveness of 2.2-MeV gamma rays could be somewhat less than that of the reference ^{60}Co gamma rays used in studies to estimate RBEs (Straume, 1995). However, we do not believe that this difference needs to be taken into account in estimating RBE factors for neutrons. The reduction in the biological effectiveness of 2.2-MeV gamma rays relative to ^{60}Co gamma rays should be less than a factor of 2 (Straume, 1995). This difference should be small compared with possible errors in estimating cancer risks that result from an assumption that the spectrum of photons to which the Japanese atomic-bomb survivors were exposed has the same biological effectiveness as ^{60}Co gamma rays. This assumption is implicit in the RBE factors for neutrons, and other radiations, developed in this report.

It also is possible that the assumed probability distributions of the RBE factors for neutrons could tend to overestimate cancer risks in humans, especially at energies greater than about 0.1 MeV. In studies in small mammals that were used to estimate RBEs for fission neutrons, a substantial fraction of the dose to target tissues was delivered by high-LET radiations (e.g., recoil protons). In humans, however, more of the dose to deep-lying organs and tissues would be delivered by gamma rays produced by neutron interactions in tissue. Therefore, RBEs obtained from studies in small mammals should tend to overestimate the biological effectiveness of incident fission neutrons in most organs and tissues of humans (ICRP, 1997; Edwards, 1997; Edwards, 1999). However, we have not adjusted the RBE factors for neutrons to account for possible differences in biological effectiveness in humans compared with small mammals, mainly because calculations indicate that this difference depends in a complicated way on the neutron energy, the particular target tissue, and the irradiation geometry (ICRP, 1997). We have accounted for such differences only in a general way by defining probability distributions of the RBE factors for neutrons to include values as low as 1.0.

RBE FACTOR FOR ALPHA PARTICLES

Approach to Estimating RBEs

Like neutrons, alpha particles are high-LET radiations that have been shown to be considerably more effective than low-LET radiations in inducing stochastic responses in biological systems. Alpha particles also are presumed to have a linear dose-response relationship at doses below those where significant cell killing occurs. Thus, in principle, it would be desirable to estimate cancer risks in humans exposed to alpha particles based on estimates of RBE at high acute doses of high-energy gamma radiation, RBE_H, in accordance with eq. (3), as we have done for neutrons, to lessen the influence of variations in the DDREF of the reference radiation. The importance of the DDREF of the reference radiation is indicated by the pronounced increase in RBEs with decreasing dose of alpha particles in the studies summarized in Fig. 9. As is the case with neutrons, high estimates of RBEs at low doses, RBE_M, may be due, at least in part, to high values of DDREF for the reference radiation.

As discussed below, however, most studies of alpha particles did not use high acute doses of gamma rays as the reference radiation. Furthermore, an analysis to estimate RBEs for alpha particles at high acute doses of the reference radiation, similar to the analysis for neutrons by Edwards (1997; 1999), has not, to our knowledge, been performed. Such an analysis is not straightforward, due to the dependence of the DDREF of the reference radiation on the chosen value of a high dose (see Fig. 5). Therefore, for alpha particles, we developed a probability distribution of the RBE factor at low doses and dose rates of the reference radiation, $\overline{RBE}_M$, for use in eq. (2). This distribution is based on estimates of RBE_M obtained from various studies.

Alpha particles are somewhat simpler than neutrons in that the range of energies that occur in radioactive decay is limited. A calculation of the energy dependence of the effective quality factor by the ICRU (1986), shown in Fig. 10, indicates that the biological effectiveness of alpha particles is nearly independent of energy over the energy range of concern. We have assumed that a single probability distribution of the RBE factor can be applied to all alpha particles that occur in radioactive decay.

Development of RBE Factor

Data on RBEs for alpha particles emitted in the decay of radionuclides have been reviewed by the NCRP (1990) and the NRPB (Muirhead et al., 1993); see also Sinclair (1996). Compared with neutrons, estimation of RBEs for alpha particles is complicated by the fact that the reference radiation in most studies was not high-energy gamma rays. In some studies in mammalian cell systems, the reference radiation was *X* rays, and in studies of induction of bone or lung tumors in mammals, the reference radiation usually was the continuous spectrum of beta particles emitted in the decays of ^{90}Sr and ^{90}Y or other radionuclides. However, the difference between using electrons from beta decay and high-energy gamma rays as the reference radiation may not be significant, because studies discussed in Section 7.3 of NCRP (1990) indicated that

beta particles from ^{144}Ce decay and protracted ^{60}Co gamma rays are equally effective in producing chromosome aberrations in the liver of hamsters.

The derivation of RBEs from studies comparing induction of bone tumors in mammals by alpha-emitting radionuclides relative to ^{90}Sr and ^{90}Y is further complicated by differences in the distributions of the study and reference radionuclides in cortical and trabecular bone compared with bone surfaces. These differences are important because the radiosensitive tissues in bone are located near the surface. For example, ^{239}Pu appears to be approximately 15 times more effective in inducing bone tumors in mice and dogs than ^{226}Ra when toxicity is estimated based on the average skeletal dose (NCRP, 1990). However, this difference is due mainly to the fact that radium deposited in the skeleton is distributed throughout the volume of bone, as is strontium, but plutonium remains near the sites of deposition on bone surfaces. Similar effects are shown in studies of the toxicity of other alpha-emitting radionuclides in bone including, for example, ^{241}Am and $^{243,244}Cm$ (NCRP, 1990).

Estimates of RBE_M for alpha particles obtained from reviews and analyses by the NCRP (1990) and the NRPB (Muirhead et al., 1993) are summarized in Table 7. Estimates obtained in an earlier analysis by the ICRP (1980) also are summarized. The values in Table 7 are central estimates, and they vary from less than 5 to nearly 100 (see footnote b).

Based on the estimates of RBE_M in Table 7, and taking into account that there is uncertainty in each estimate, we describe the RBE factor for alpha particles at low doses and dose rates of the reference radiation, $\overline{RBE}_M$, by a stepwise-uniform probability distribution having 15% of the values in the range of 1.0-10, 25% in the range of 10-20, 30% in the range of 20-30, 20% in the range of 30-40, 7.5% in the range of 40-60, and 2.5% in the range of 60-100. This distribution has a median of 23, an arithmetic mean of 25, and a 95% confidence interval between 2.5 and 60. This probability distribution also provides a reasonable representation of the estimates of RBE_M for animal tumors only. The assumed probability distribution of $\overline{RBE}_M$ encompasses the recommended point values of the effective quality factor, $\overline{Q}$, and the radiation weighing factor, w_R, for alpha particles given Table 1.[13]

The stepwise-uniform probability distribution described above was chosen to represent the RBE factor for alpha particles based on the following considerations. The distribution of the values of RBE_M summarized in Table 7 is approximately symmetrical about a central value. The estimates of RBE_M also suggest that substantial weight should be given to values toward the extremes of the distribution, especially values toward the lower end. We give less weight to values toward the upper end of the distribution based on the consideration that estimates in the range of about 60-100 for inhalation of insoluble ^{239}Pu oxide obtained in an analysis of early studies by the ICRP (1980) were not seen in more recent studies. We also note that the

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[13]The point values of $w_R = 20$ and $\overline{Q} = 25$ in Table 1 are at the 40th and 55th percentiles, respectively, of the probability distribution of $\overline{RBE}_M$. An estimated RBE_M for inhaled alpha-emitting radionuclides of 30 derived by the ICRP (1980) from studies in animals is at the 70th percentile.

distribution of values in Table 7 is not described nearly as well by other commonly assumed probability distributions, such as lognormal or triangular. Since the probability distribution of the RBE factor has a specified lower bound of 1.0, truncation of the lower tail at 1.0 is not needed, in contrast to the case of neutrons discussed previously.

With the exception of exposure to radon and its short-lived decay products noted in the Introduction, the probability distribution of $\overline{RBE}_M$ described above is used to estimate cancer risks in humans at low doses and dose rates of alpha particles in accordance with eq. (2). Since alpha-emitting radionuclides of concern in exposures of workers and the public, excluding radon, have half-lives of at least 0.5 years and are tenaciously retained in the body, acute exposure to alpha particles emitted by inhaled or ingested radionuclides should not be of concern. External exposure generally is not a concern for alpha particles emitted by radionuclides.

Consideration of Cancer-Specific RBEs

The probability distribution of the RBE factor for alpha particles described above is intended to be applied to all cancers. There is some indication from studies in humans that the RBE for leukemia is less than the RBE for other cancers. Based on an estimated lifetime risk of leukemia of (5-6) $\times 10^{-3}$ Gy^{-1} in patients who were administered Thorotrast[14] (National Research Council, 1988) compared with an estimate of 5×10^{-3} Gy^{-1} at low doses and low dose rates of low-LET radiation, the U.S. Environmental Protection Agency (EPA) concluded that the "effective RBE" of alpha particles for leukemia is essentially unity (EPA, 1994; Eckerman et al., 1999). However, there are several possible difficulties with this interpretation. First, as noted by the EPA (1994), the lower than expected leukemia risk in the Thorotrast patients may result from a nonuniform distribution of dose within bone marrow such that average doses to sensitive target cells are substantially lower than calculated average doses to bone marrow.

Second, calculated doses to bone marrow are highly sensitive to assumptions about the distribution of alpha-emitting radionuclides on bone surfaces and in the volume of cortical and trabecular bone (Eckerman et al., 1999). This is an important consideration for ^{232}Th because thorium remains at the sites of deposition on bone surfaces but its ^{228}Ra decay product, which decays to the alpha-emitting radionuclides ^{228}Th and ^{224}Ra, is distributed in bone volume. Thus, estimated doses to bone marrow are sensitive to the assumed rate of transfer of ^{228}Ra from bone surfaces. More generally, estimates of marrow dose from alpha-emitting radionuclides deposited in the skeleton have large uncertainties that are not taken into account in the estimated risks to Thorotrast patients. For example, Hunacek and Kathren (1995) noted that reported doses to bone marrow of these patients vary by a factor of about 10, with the result that the estimated risk of leukemia ranges from 5×10^{-3} to 6×10^{-2} Gy^{-1}; the best estimate given by Hunacek and Kathren is 3×10^{-2} Gy^{-1}. Such higher risks, when compared with the estimated risk from exposure to low-LET radiation, indicate that the RBE of alpha particles is substantially greater than unity.

[14]Thorotrast is a colloidal form of thorium oxide.

Third, the estimated risk of leukemia at low doses and dose rates of low-LET radiation is based on data in the Japanese atomic-bomb survivors who received a mean absorbed dose of gamma rays of 0.25 Gy (UNSCEAR, 2000), whereas estimated doses to bone marrow from alpha particles in the Thorotrast patients are about 1 Gy or higher (National Research Council, 1988; Hunacek and Kathren, 1995). At such high doses of alpha particles, the risk of leukemia may be influenced by the effect of cell killing in bone marrow (Muirhead et al., 1993).

Finally, data on RBEs for fission neutrons discussed in the previous section do not support an assumption that the RBE for leukemias from exposure to alpha particles is less than RBEs for other cancers by a factor of 10 or more. Data on RBEs for fission neutrons are relevant because a large difference in the biological effectiveness of alpha particles and fission neutrons is not expected and has not been demonstrated experimentally (ICRU, 1986; Sinclair, 1985).

Based on these considerations and an absence of supporting information from other studies of alpha particles, we have not developed separate probability distributions of the RBE factor for leukemia and other cancers. We have accounted for the possibility of a substantially lower RBE for leukemia compared with other cancers only in a general way by defining the probability distribution of $\overline{RBE}_M$ for alpha particles so that a substantial weight is given to values in the range of 1-10.

Correction for Inverse Dose-Rate Effect

As in the case of neutrons discussed in the previous section, an additional consideration in estimating cancer risks at low doses and dose rates of alpha particles is the possibility of an inverse dose-rate effect, whereby the biological effectiveness at a given dose increases as the dose rate decreases. An analysis of data in humans (underground miners) who were exposed to elevated levels of radon has shown an inverse dose-rate effect that could be as much as a factor of 3 but is more likely less than a factor 2 (Lubin et al., 1995).

Arguments can be made both for and against the need to account for a possible inverse dose-rate effect in estimating cancer risks from chronic exposure to alpha particles. An argument in favor is that since an inverse dose-rate effect has been observed in some studies of neutrons, the effect, if it exists, also should occur with other high-LET radiations. However, there are several counter-arguments to this view. First, an inverse dose-rate effect is not observed in underground miners at exposures to radon decay products less than 50 Working Level Months (WLM) (Lubin et al., 1995).[15] Second, in contrast to studies of neutrons in small mammals, all studies using alpha-emitting radionuclides involved protracted exposures, and the estimated RBEs may already account for an inverse dose-rate effect. Finally, again in contrast to neutrons, the RBEs for alpha particles are extrapolated values at low doses and dose rates, RBE_M, and the

[15]Based on conversion coefficients given in Table 4 of ICRP (1987) and Table 6 of ICRP (1993), an exposure of 50 WLM corresponds to an absorbed dose to the bronchial epithelium, where lung carcinomas in the underground miners are observed to originate, of about 0.8 Gy.

highest values, which correspond to the highest DDREFs of the reference low-LET radiations, may result in overestimates of cancer risks in humans.

Based on these arguments, we assume that the probability distribution of the RBE factor for alpha particles described previously should be adjusted by a small factor that represents the inverse dose-rate effect, to be consistent with an assumption of this effect in cases of chronic exposure to neutrons. However, we give less weight to a possible inverse dose-rate effect for alpha particles than for neutrons based mainly on two considerations discussed above. First, the data on underground miners do not show an effect at low doses of concern in routine exposures of workers and the public. Second, the probability distribution of the RBE factor may already incorporate an inverse dose-rate effect when the relevant studies involved protracted exposures to alpha particles. Specifically, we assume a discrete probability distribution for the enhancement factor representing the inverse dose-rate effect for alpha particles with 70% of the values at 1.0, 20% at 1.5, 7.5% at 2.0, and 2.5% at 3.0. The arithmetic mean of this distribution is about 1.2.

Summary

Cancer risks in humans from exposure to alpha particles emitted by radionuclides are estimated using an approach represented by eq. (2). Specifically, the risk per unit absorbed dose from exposure to alpha particles (α) is estimated as

$$R_\alpha = \overline{\mathrm{RBE}}_{\alpha,\mathrm{M}} \times \mathrm{EF}_\alpha \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_\gamma}, \qquad (6)$$

where $\overline{\mathrm{RBE}}_{\alpha,\mathrm{M}}$ is the RBE factor for alpha particles at low doses and dose rates, EF_α is an enhancement factor that represents the inverse dose-rate effect for chronic exposure to alpha particles, $R_{\gamma,\mathrm{H}}$ is the risk per unit dose at high doses and high dose rates of gamma rays, and DDREF_γ is the dose and dose-rate effectiveness factor for gamma rays and other low-LET radiations. Since exposures to alpha-emitting radionuclides are assumed to be chronic, the enhancement factor is applied in all such cases. Truncation of the aggregate probability distribution of $\overline{\mathrm{RBE}}_{\alpha,\mathrm{M}} \times \mathrm{EF}_\alpha$ at 1.0, consistent with the approach for neutrons discussed previously, is not needed, because this distribution does not include values less than 1.0. As noted in the Introduction, eq. (6) applies to all exposures to alpha particles emitted by radionuclides, except inhalation of radon and its short-lived decay products.

RBE FACTORS FOR PHOTONS

Approach to Estimating RBEs

Compared with neutrons, alpha particles, and beta particles from decay of ^{3}H, there are few measurements of the biological effectiveness of orthovoltage *X* rays (and other lower-energy

photons) relative to high-energy gamma rays. Furthermore, a review by the NCRP (1990) indicates that only a single stochastic endpoint in mammalian systems (induction of dicentric chromosomes in human lymphocytes) has been widely studied in investigating the biological effectiveness of *X* rays. Nonetheless, we believe that the available data on chromosome aberrations, supplemented by information obtained from studies of other radiations discussed in this section, provide sufficient evidence to support an assumption that lower-energy photons have a substantially greater biological effectiveness than high-energy gamma rays. As noted in the Introduction, the ICRU (1986) reached the same conclusion. This assumption applies to orthovoltage *X* rays and other photons of similar energies including, for example, the 60-keV gamma ray emitted in decay of ^{241}Am.

In estimating cancer risks in humans from exposure to X rays and other lower-energy photons, the approach represented by eq. (2), which applies at low doses and low dose rates, is used. An analysis to estimate RBEs at high doses and high dose rates of photons, $RBE_{\gamma,H}$, similar to the analysis for neutrons by Edwards (1997; 1999) discussed previously, has not, to our knowledge, been performed. An additional complication that discourages the use of RBEs at high doses and high dose rates and an approach to estimating risks represented by eq. (3) is that the reference gamma rays and the *X* rays under study both exhibit non-linear dose-response relationships. As a consequence, the DDREFs for the two radiations in a given study often differ substantially from each other and from the nominal value of 2 normally used in radiation protection (ICRP, 1991; NCRP, 1993), and the DDREFs for the two radiations also vary from one study to another. Therefore, the following discussion focuses on the estimation of RBEs for lower-energy photons at low doses and low dose rates, $RBE_{\gamma,M}$.

Development of RBE Factor

Studies of the biological effectiveness of 220-250 kVp *X* rays in inducing dicentric chromosomes in human lymphocytes were reviewed and evaluated by the NCRP (1990). The average *X*-ray energy in these studies was about 50-65 keV (Stanton et al., 1979; NCRP, 1985). The dose-response relationships for the *X* rays and reference gamma rays in these studies were assumed to be linear-quadratic; i.e., the response was assumed to be described by $\alpha D + \beta D^2$, where D is the absorbed dose and α and β are coefficients obtained from fits to the data. The data on dose-response for the *X* rays and reference gamma rays in the various studies are summarized in Table 8. Point estimates of RBE_M, calculated by the NCRP (1990) as α_X/α_γ using the central estimates of the two coefficients in Table 8, are given in Table 9. Similar values of RBE_M for *X* rays are indicated when estimates of RBE_M for neutrons for the same endpoint obtained in studies using *X* rays as the reference radiation are compared with estimates obtained using ^{60}Co gamma rays (Dobson et al., 1991; Schmid et al., 2000).

The NCRP's point estimates of RBE_M in Table 9 do not take into account the reported uncertainties in the coefficients α_X and α_γ. We estimated the uncertainty in each value of RBE_M in the following way. We assumed that the central estimates and standard errors of α_X and α_γ given in Table 8 define 68% confidence intervals of lognormal probability distributions of these

coefficients.[16] We then used random sampling methods to calculate the probability distribution of RBE_M as the ratio of the distributions of α_X and α_γ, and the 68% confidence interval of this distribution was obtained. These confidence intervals are given in parentheses in Table 9.

The estimates of RBE_M for *X* rays and their uncertainties summarized in Table 9 can be represented reasonably well by a lognormal probability distribution having a 95% confidence interval between 1.0 and 6.5. However, information obtained from other studies also should be taken into account. This information is indirect, in that the radiation under study was not *X* rays or gamma rays but both of these radiations were used as reference radiations. Inferences about the biological effectiveness of *X* rays relative to gamma rays can be made by comparing RBEs for the radiation under study relative to *X* rays with RBEs relative to gamma rays, provided the values apply to similar endpoints. Information obtained from various studies, mostly reviews by experts and expert groups, is summarized below.

- A study of induced pink mutation events in stamen hairs of *Tradescantia* (Underbrink et al., 1970) discussed in Section 2.2.4 of NCRP (1990), in which the radiations under study were neutrons, indicated that the RBE of *X* rays was about 1.7.

- Studies of mutations in human diploid fibroplasts (Cox et al., 1977; Hei et al., 1988) summarized in Fig. 3.13 of NCRP (1990), in which the radiations under study included protons, deuterons, and ions of ^3He, ^4He, ^{10}B, and ^{14}N, indicated that the RBE of *X* rays was about 3 or less.

- A study of dominant lethal mutations in cells of mice (Pomerantseva, 1964) discussed in Section 4.1.1.1 of NCRP (1990), in which the radiation under study was high-energy protons, indicated that the RBE of *X* rays was about 1.5.

- A study of life-shortening in mice (Upton et al., 1967) summarized in Table 8.2 of NCRP (1990), in which the radiations under study were neutrons, indicated that the RBE at low doses and low dose rates of *X* rays was about 3 or less. A similar result was obtained from an analysis of these data by Edwards (1999) to obtain estimates of RBE for neutrons at high acute doses of the reference radiation, RBE_H (see Table 3).

- A study of mutations in human lung fibroplasts (Cox and Masson, 1979) summarized in Section 7, Paragraph 19, and Table 7.3 of Muirhead et al. (1993), in which the radiations under study were alpha particles, indicated that the RBE of *X* rays was about 2.5 when compared with the results of a study of mutations in Chinese hamster cells (Thacker et al., 1979) summarized in Table 7.

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[16]Uncertainties are described by lognormal probability distributions to avoid problems that arise in calculating the ratio of two normal distributions when very small or negative values of the probability distribution in the denominator are randomly sampled.

- Several inferences can be made from studies of the biological effectiveness of low-energy beta particles from ^3H decay summarized by Straume and Carsten (1993) and discussed in the following section. Studies of carcinogenesis endpoints in mammals and mammalian cells indicated that the RBE of *X* rays was less than 2 (see Table 10). Studies of genetic endpoints in mammalian systems and fish lymphocytes indicated that the RBE of *X* rays was about 1.6 on average and did not exceed about 3.5 (see Table 11). A study of chromosome aberrations in human lymphocytes indicated that the 68% confidence interval of the RBE for *X* rays was (2.3, 3.9) (see Table 12); this estimate applies to the same endpoint as the results summarized in Table 9. Results of studies of reproductive effects in small mammals and fish summarized in Table 7 of Straume and Carsten (1993) are not considered, because these endpoints are deterministic and, thus, are not considered to be relevant in estimating cancer risks in humans.

- A study of tumor induction in rats (Wolf et al., 2000), in which the radiation under study was fission neutrons, indicated that the RBE of *X* rays at acute doses of 2 Gy was about 3. This RBE should be especially relevant to estimating cancer risks in humans.

The indirect estimates of RBE summarized above suggest that a lognormal probability distribution of RBE_M for *X* rays and other lower-energy photons having a 95% confidence interval between 1.0 and 6.5 gives too much weight to relatively high values. We believe that this conclusion is reasonable even though uncertainties in the indirect estimates undoubtedly are substantial. We also note that the highest values of RBE_M in Table 9 have the largest uncertainties, which indicates that these values should be given less weight compared with the lower, and less uncertain, estimates of RBE_M for the same endpoint. Based on this information, we reduce the upper confidence limit of the lognormal probability distribution of RBE_M obtained from studies of dicentric chromosomes in human lymphocytes from 6.5 to 5.0. Thus, the lognormal probability distribution of RBE_M that is assumed to describe all the radiobiological data discussed above has a 95% confidence interval between 1.0 and 5.0. This distribution has a geometric mean and geometric standard deviation of 2.2 and 1.5, respectively, and an arithmetic mean of 2.4. The distribution assigns a small weight to an assumption that the biological effectiveness of *X* rays and other lower-energy photons is the same as that of high-energy gamma rays, and to an assumption that values greater than 5 are possible. Neither of these assumptions can be ruled out by the available radiobiological data.

We then investigated whether useful information on the biological effectiveness of *X* rays relative to high-energy gamma rays can be obtained from epidemiological studies of human populations. In particular, estimated risks of thyroid cancer in children exposed to *X* rays can be compared with estimated risks of thyroid cancer in the Japanese atomic-bomb survivors who were exposed in childhood mainly to high-energy gamma rays. For the atomic-bomb survivors, the following central estimates and 95% confidence intervals (in parentheses) of the excess relative risk of thyroid cancer per Gy in children have been reported: